B2

26. (Amended) The method of claim 22, wherein said arthritis-related tissue inflammation is selected from the group consisting of connective tissue inflammation, joint inflammation, and synovium inflammation.

REMARKS

The instant invention is drawn *inter alia* to methods of treating arthritis using androstenediones.

Claims 30 and 33-38 have been cancelled without prejudice to future prosecution. Claims 22 and 26 have been amended to more fully identify the claimed invention. Support for the amendment to claim 22 can be found in claims 7 and 11, for example. Support for the amendment to claim 26 can be found, for example, on page 1, lines 14-19 and on page 2, lines 20-25 of the specification.

The amendments to the claims are fully supported by the application as filed and add no new matter. Attached hereto is a marked up version of the changes made to the specification by the instant Amendment captioned "Version with Markings to Show Changes Made".

Claim Objections - 37 C.F.R. § 1.75(c)

Claims 22-30 stand rejected under 37 C.F.R. § 1.75(c) as allegedly being of improper dependent form. The Examiner states that the "recitation of "tissue inflammation" in claim 22 fails to further limit the method recited in claim 1 or 2." Applicant respectfully traverses this rejection as it applies to the claims as amended.

Claim 22 now states "arthritis-related tissue inflammation" so as to clarify that the inflammation must be related to the arthritic condition rather than the result of a disease or injury unrelated to arthritis. Since this is a specific symptom of arthritis, claim 22 does further limit the method recited in claims 1 and 2. Therefore, Applicant respectfully requests that the objection be withdrawn and the claims be allowed.

Claim Rejections - 35 U.S.C. § 112

Claims 7, 11, 26 and 30 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. The Examiner states that the phrase "patient afflicted with arthritis-related tissue inflammation" in claims 7 and 26 and "patient diagnosed with arthritis-related tissue inflammation" in claims 11 and 30 renders the claims indefinite as to what patients are encompassed by the claims. Applicant respectfully traverses this rejection as it applies to the claims as amended.

Claim 30 has been cancelled rendering this rejection moot as to that claim. Claim 26 has been amended to identify specific types of arthritis-related inflammation also rendering the rejection moot as it applies to that claim. However, the rejection is discussed as it applies to claims 7 and 11 and claim 22, which has been amended to include the phrase "arthritis-related tissue inflammation".

Applicant respectfully requests clarification as to the confusion over the patients encompassed by the claims. The patients are those in need of arthritis treatment who have inflammation related to their arthritic condition or who are diagnosed with inflammation related to their arthritic condition. This phrasing indicates that the inflammation is not the result of a disease or injury unrelated to arthritis.

In the absence of clarification as to what exactly is unclear in the wording of the claims, Applicant respectfully requests that the indefiniteness rejection under 35 U.S.C. § 112, second paragraph be withdrawn and that the claims be allowed.

Claim Rejections - 35 U.S.C. § 103

Claims 1-11 and 22-38 stand rejected under 35 U.S.C. § 103(a) for alleged obviousness over Lardy in view of Peat (U.S. Patent 4,628,052). Applicant respectfully traverses this rejection.

Three criteria must be met to establish a case of *prima facie* obviousness: (1) there must be some suggestion or motivation to modify or combine references, (2) there must be a reasonable expectation of success, and (3) the references must teach or suggest all the claim limitations. The teaching or suggestion to make the combination and the reasonable expectation of success must both be found in the cited art, not the applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991). These criteria are not met for the claimed invention.

The claimed invention is drawn *inter alia* to methods of treating arthritis by administering Δ5-androstene-3β-ol-7,17-dione and β esters thereof. These compounds are essentially incapable of being metabolized to androgens, estrogens or dehydroepiandrosterone (DHEA) (See, for example, page 4, lines 18-22 of the specification).

A reasonable reading of the cited references (Lardy and Peat) indicates that taken together they satisfy none of the three criteria stated above.

First, the references do not teach or suggest all the claim limitations. Peat describes the use of DHEA for arthritis. DHEA is the major androgen precursor in men and women (see, for example, page 3, lines 21-22 in the specification). Lardy teaches *inter alia* that DHEA has some ability to improve antibody responsiveness of the immune system, but significantly less than Δ5-androstene-3β-ol-7,17-dione (see, for example, column 10, lines 31-33).

Taken together, Peat and Lardy teach treating arthritis using a compound (DHEA) with significant androgenic ability and some immune stimulating ability. The claimed compound, Δ5-androstene-3β-ol-7,17-dione, does not satisfy those criteria. In fact, its strengths are the opposite of DHEA's. Δ5-androstene-3β-ol-7,17-dione has essentially no androgenic ability and significant immune stimulating ability. Thus, the cited

references do not teach or suggest all the claim limitations of a compound without androgenic potential and with immuno-stimulatory potential. Therefore, the Examiner has failed to make a prima facie case for obviousness, and this rejection cannot stand.

Second, there is no suggestion or motivation to modify or combine references. The Examiner states that the motivation to use Δ5-androstene-3β-ol-7,17-dione in place of DHEA to treat arthritis arises from their structural similarity and similar pharmacological activities (page 5, last paragraph of the Office Action).

However, DHEA and Δ5-androstene-3β-ol-7,17-dione do not have similar pharmacological activities. Two compounds clearly do not have similar pharmacological activities when one, DHEA, is the major androgen precursor in humans, and the other, Δ5-androstene-3β-ol-7,17-dione, is not metabolizable to androgens. That is an enormous difference that has a significant impact on their pharmacological activity. This fact is something that the Examiner has failed to respond to when claiming the compounds have similar pharmacologic activities. In addition, Δ5-androstene-3β-ol-7,17-dione has superior immune stimulating ability compared to DHEA.

Third, the references do not indicate that there is a reasonable expectation of success. Peat teaches the use of a compound, DHEA, with superior androgenic activity and inferior immuno-stimulatory ability. In rheumatoid arthritis (RA), for example, androgen levels are low in both men and women. In addition, RA is characterized by striking age-sex disparities, which also suggests that androgens play a role in RA. (See, for example, page 3, lines 16-31 of the specification.) Thus, one of ordinary skill in the art would be likely to conclude that DHEA's activity may well be the result of its androgenic ability, not its immuno-stimulatory ability. Thus, Peat does not suggest a

reasonable expectation of success for a compound, Δ5-androstene-3β-ol-7,17-dione, that has no androgenic ability.

Further, despite the Examiner's comments to the contrary, enhancing immune function and particularly improving the immune response to an antigen, is counterintuitive as a treatment for arthritis as discussed more fully in the previous Response dated April 3, 2002. Although DHEA has some immunologic ability, it is less than that of Δ5-androstene-3β-ol-7,17-dione. Even if some immune enhancement is not counter productive to treatment, taken as a whole there is no reason to believe that more is better.

Accordingly, based on Lardy, one of ordinary skill in the art would expect that administration of Δ5-androstene-3β-ol-7,17-dione (an immune enhancer with no androgenic ability) would exacerbate, rather than treat, arthritis. Such a teaching away from the claimed invention is a significant factor to be considered in determining obviousness and cannot be ignored.

Thus, taken as a whole, the cited art does not indicate a reasonable expectation of success.

In summary, the requirement for making a prima facie case of obviousness has not been met. In view of the above, Applicant respectfully requests that the obviousness rejection under 35 U.S.C. § 103(a) be withdrawn and that the claims be allowed.

SUMMARY

Applicants assert that the claimed invention is in condition for allowance and notification to that effect is respectfully requested. In order to facilitate rapid allowance, the Examiner is invited to contact the undersigned at the telephone number below.

Any fees due in relation to the timely filing of this Response are hereby authorized to be deducted from Deposit Account No. 501536.

Respectfully submitted,

Date: Dec. 13, 2002

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

22. (Amended) The method of either one of claims 1 and 2, wherein said one or more symptoms of arthritis are selected from the group consisting of arthritis-related tissue inflammation, joint pain, joint stiffness, inability to move a joint normally, nodules, and swelling.

26. (Amended) The method of claim 22, wherein said [patient is afflicted with] arthritis-related tissue inflammation is selected from the group consisting of connective tissue inflammation, joint inflammation, and synovium inflammation.